

Abnormal And Euthyroid Ranges Of Thyroid Hormones In Serum And Liver Cancer Mortality: A Cohort Study

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INTRODUCTION

Thyroid hormone is a key regulator of cellular processes in the human body. It controls cell proliferation, differentiation, apoptosis, and metabolism and has been reported to have both tumor-promoting and suppressing effects. Hypothyroidism is related to obesity, insulin resistance, hyperlipidemia, and lipid peroxidation, which are all contributors of liver damage, and can also directly affect liver health.

The impact of serum thyroid hormone concentration on the risk of hepatocellular carcinoma remains unclear.

AIM

We examined the association of serum thyrotropin (TSH) and thyroid hormone concentration with liver cancer mortality in a large cohort of liver cancer-free individuals.

METHOD

A cohort study was performed with 517,996 Korean adults who were free from liver cancer at baseline and underwent a health examination to determine levels of free thyroxine (FT4) and TSH and were followed for up to 16 years.

Vital status and mortality from liver cancer were ascertained through National Death Records. Liver cancer mortality was defined as death with an underlying cause of ICD-10 C22, which is malignant neoplasm of the liver and intrahepatic bile ducts.

A Cox proportional hazard model was used to estimate the adjusted hazard ratio (aHR) and 95% confidence interval (CI).

Adjusted variables were sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, body mass index, education level, and family history of cancer, viral hepatitis, fatty liver, liver cirrhosis, diabetes, hypertension, and lipid profile.

RESULTS

The mean age of study participants at baseline was 39.1 years (standard deviation, 10.4; median, 36; interquartile range 31-44; range 18-94) and 53.7% were male.

During 4,457,095 person-years of follow-up, 376 liver cancer deaths were identified (liver cancer mortality rate of 8.4 per 10⁵ person-years). The median follow-up was 8.1 years (maximum, 16 years; interquartile range, 4.9–12.4 years).

Subjects with low FT4 levels were associated with an increased risk of liver cancer mortality with a corresponding multivariable aHR 2.25 (95% CI: 1.62-3.12) compared to those with normal FT4 levels.

Multivariable model was adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, BMI, education level, and family history of cancer, viral hepatitis, fatty liver, liver cirrhosis, and FIB-4.

Within the euthyroid range (n = 495,202), there was also a dose-dependent inverse relationship between FT4 level and liver cancer mortality (p < 0.001). Within the euthyroid range a 0.1-unit increase in FT4 level was significantly and inversely related to liver cancer mortality with HR (95% CI) of 0.85 (0.79–0.92).

Being euthyroid was defined as having levels of TSH and FT4 within their corresponding normal ranges, no history of thyroid disease, and not currently being treated for thyroid medications.

CONCLUSIONS

In this large cohort, the risk of liver cancer mortality increased as both abnormal and normal thyroid levels of FT4 decreased. Our findings indicate that thyroid function within both the abnormal and normal ranges may affect liver cancer mortality.

TABLE 1. Estimated[†] mean values (95% CI) and adjusted^a proportion (95% CI) of baseline characteristics of study participants by liver cancer mortality

Characteristics	Liver cancer mortality (-)	Liver cancer mortality (+)	P value
Number	517,620	376	
Age (years)	39.0 (39.0-39.1)	54.9 (53.8-55.9)	< .001
Male (%)	53.6 (53.5-53.8)	82.9 (79.1-86.7)	< .001
BMI (kg/m ²)	23.3 (23.3-23.4)	23.9 (23.6-24.2)	.001
Current smoker (%)	24.4 (24.3-24.5)	30.2 (26.7-33.7)	.001
Alcohol intake (%) [§]	18.3 (18.2-18.4)	16.7 (13.6-19.8)	.322
Regular exercise (%) [¶]	15.0 (14.9-15.1)	14.0 (11.0-17.1)	.551
High education level (%)	72.5 (72.3-72.6)	58.7 (53.2-64.2)	< .001
Diabetes (%)	3.9 (3.8-3.9)	5.4 (4.1-6.6)	.008
Hypertension (%)	15.0 (14.9-15.1)	13.8 (11.5-16.1)	.319
HBV (%)	3.6 (3.6-3.7)	53.4 (48.3-58.5)	< .001
HCV (%)	0.18 (0.17-0.19)	2.6 (1.6-3.6)	< .001
Cirrhosis (%)	0.0 (0.0-0.0)	2.4 (1.5-3.4)	< .001
Fatty liver (%)	26.6 (26.5-26.8)	9.9 (7.7-12.1)	< .001
Glucose (mg/dL)	94.7 (94.7-94.8)	96.2 (94.6-97.8)	.066
Total cholesterol (mg/dL)	194.0 (193.9-194.1)	176.2 (172.8-179.7)	< .001
LDL-C (mg/dL)	115.4 (115.3-115.5)	97.1 (94.1-100.1)	< .001
HDL-C (mg/dL)	57.1 (57.0-57.1)	59.5 (58.1-60.8)	< .001
Triglycerides (mg/dL)	118.7 (118.5-118.9)	86.8 (78.9-94.6)	< .001
AST (U/L)	23.8 (23.7-23.8)	49.2 (47.3-51.1)	< .001
ALT (U/L)	25.1 (25.1-25.2)	47.6 (45.1-50.1)	< .001
GGT (U/L)	30.4 (30.3-30.5)	99.7 (95.7-103.7)	< .001
HOMA-IR	1.74 (1.74-1.74)	2.37 (2.25-2.50)	< .001
FT3 (pg/mL) ^{††}	3.24 (3.23-3.24)	3.13 (2.97-3.28)	.167
FT4 (ng/dL)	1.28 (1.28-1.28)	1.21 (1.16-1.25)	.002
TSH (μIU/mL)	2.29 (2.28-2.30)	2.27 (1.62-2.92)	.958
FIB4	0.81 (0.81-0.81)	2.55 (2.51-2.59)	< .001
APRI	0.28 (0.27-0.27)	1.01 (0.98-1.04)	< .001

^aAbbreviations: ALT, alanine aminotransferase; APRI, aspartate transaminase to platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; FT3, free triiodothyronine; FT4, free thyroxine; GGT, gamma-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; TSH, thyroid-stimulating hormone.

[†]Adjusted for age and sex

^{||}BMI ≥ 25 kg/m²; [§]≥20 g/day; [¶]≥ 3 times/week; ^{||}≥ College graduate

TABLE 2. Hazard ratios (95% CIs) for liver cancer mortality by baseline thyroid hormone level in the overall population (n = 517,996)

	Mortality rate (10 ⁵ Person-years)	Age and sex-adjusted HR (95% CI)	Multivariable-adjusted HR [†] (95% CI)
TSH (μIU/mL)			
Low (n = 5,696)	3.9	0.54 (0.13-2.16)	0.68 (0.17-2.71)
Normal (n = 495,202)	8.5	1.00 (reference)	1.00 (reference)
High (n = 17,098)	9.6	1.04 (0.58-1.86)	1.10 (0.61-1.96)
P for trend		.565	.590
FT4 (ng/dL)			
Low (n = 9,812)	46.2	4.43 (3.22-6.10)	2.25 (1.62-3.12)
Normal (n = 499,493)	7.7	1.00 (reference)	1.00 (reference)
High (n = 8,691)	1.3	0.19 (0.03-1.38)	0.31 (0.04-2.18)
P for trend		< .001	< .001

[†]Multivariable model was adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, regular exercise, BMI, education level, and family history of cancer, viral hepatitis, fatty liver, liver cirrhosis, and FIB4.

TABLE 3. Hazard ratios (95% CIs) for liver cancer mortality baseline thyroid hormone level within the euthyroid range (n = 495,202)

	Mortality rate (10 ⁵ Person-years)	Age and sex-adjusted HR (95% CI)	Multivariable-adjusted HR [†] (95% CI)
TSH (μIU/mL)			
Tertile 1	8.3	1.00 (reference)	1.00 (reference)
Tertile 2	7.1	0.90 (0.69-1.17)	0.84 (0.65-1.10)
Tertile 3	9.8	1.20 (0.93-1.53)	1.14 (0.88-1.46)
P for trend		.135	.273
Per 0.1 unit increase		1.00 (0.99-1.01)	1.00 (0.99-1.01)
FT4 (ng/dL)			
Tertile 1	12.9	1.00 (reference)	1.00 (reference)
Tertile 2	5.5	0.48 (0.37-0.62)	0.63 (0.48-0.83)
Tertile 3	4.3	0.39 (0.29-0.52)	0.64 (0.48-0.87)
P for trend		< .001	.001
Per 0.1 unit increase		0.74 (0.68-0.79)	0.85 (0.79-0.92)

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